

Liver Tuberculosis in Southern Taiwan : 15-years Clinical Experience

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Abstract

Liver tuberculosis (TB) is defined as *Mycobacterium tuberculosis* infections in the liver and is usually secondary from TB of the lung or other organ. The aims of this retrospective study were to review hepatic TB diagnosed and treated in our hospital and analyze the clinical presentations, image studies and therapeutic outcomes. From January 1992 to December 2006, 1251 patients with pathological diagnosis of TB infection were admitted. Among them, ten patients (5 males and 5 females) with the diagnosis of liver TB were enrolled. The mean age of patients with hepatic TB was 52.7 years (20-76 years) . The clinical manifestations were abdominal pain (40%) , poor appetite (40%) , nausea or vomiting (40%) , fever (30%) , body weight loss (20%) . Three patients were found to have hepatic TB infection incidentally without relevant abdominal symptoms. Four patients had isolated hepatic TB and others had extra-hepatic TB infection. Coexistent pulmonary TB was found in 4 patients. Abdominal sonography and computed tomography (CT) in 9 patients revealed solitary liver tumors with or without calcification, or multiple liver tumors. Diagnostic methods included ultrasound-guided liver biopsy (50%) , laparotomy and liver biopsy or hepatectomy (50%) , positive liver TB-PCR (30%) , positive AFB stain (20%) . All 9 patients who had received complete antituberculosis therapy were cured of the disease. In conclusion, liver TB is a rare condition but curable disease. The diagnosis of liver TB is difficult due to non-specific symptoms, signs, and variations on image findings. Therefore, determination of histopathology is necessary for definite diagnosis of liver TB supplemented with TB-PCR and AFB stain. Once the diagnosis is confirmed, the disease is usually associated with good prognosis and long-term outcome under complete anti-TB treatment.(J Intern Med Taiwan 2008; 19: 410-417)

Key Words : Liver tuberculosis; Clinical presentations; Image studies; Therapeutic outcomes

Introduction

Tuberculosis (TB) is a worldwide health problem with particularly high prevalence in developing countries. As the population of human

immunodeficiency virus (HIV) infected people increases, and with the more users of immunosuppressive therapy, the incidence of TB is also increasing worldwide¹⁻³. Abdominal TB is a

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rare manifestation among various forms of extrapulmonary TB. The diagnosis of abdominal TB is made based on the demonstration of tubercle bacilli in the gastrointestinal tract, peritoneum, or intra-abdominal solid organs. The confirmation of abdominal TB is difficult to make because of its nonspecific symptoms, and it often requires invasive procedures such as laparotomy. Liver TB is considered very rare among abdominal TB patients. Usually it is associated with foci of infection in the lungs or gastrointestinal tract⁴. The diagnosis of liver TB is often overlooked because liver TB can have a relatively nonspecific clinical presentation and its lower positive acid-fast smear from liver tissue and culture rate from bile juice⁵. Therefore, it attracted our interest to perform this retrospective study on our experiences with liver TB in the past 15 years. In the current study, we analyzed the clinical presentations, image studies, pathological findings and therapeutic outcomes of liver TB.

Patients and Methods

Over a period of 15 years (January 1992 - December 2006), a total of 1251 patients with pathological diagnosis of TB infection were included from the files of the Department of Pathology, Chang Gung Memorial Hospital-Kaohsiung, Taiwan. We focused on patients with liver CT, and the diagnosis of liver TB was made based on clinical features of liver TB infection and at least one of the following criteria: (1) positive acid-fast bacilli (AFB) stain from the tissue biopsies; (2) histopathological demonstration of typically caseating granulomatous necrosis; or (3) positive polymerase chain reaction (PCR) for *M. tuberculosis* on liver tissue. We recorded the demographics and clinical manifestations, including age, sex, medical history, symptoms and signs, physical findings, laboratory and image findings (radiography and sonography) , and therapeutic

outcomes by chart review retrospectively. Patients without definite diagnosis or incomplete chart recording were excluded.

Results

This study enrolled 10 patients (5 males and 5 females) with the diagnosis of liver TB among 1251 patients with pathological diagnosis of TB infection over 15 years. The ages ranged from 20 to 76 years with a mean age of 52.7 years. The clinical manifestations in these 10 patients were abdominal pain (40%), poor appetite (40%) , nausea or vomiting (40%), fever (30%), body weight loss (20%), abdominal distension (10%), and ascites (10%). The concurrent diseases included: 5 patients with hypertension, 4 with diabetes mellitus, 2 with cancer both with end stage renal disease; chronic hepatitis B; chronic hepatitis C; old stroke; alcoholism; and ulcerative colitis. None of them was HIV-infected.

Hepatic TB infections were found incidentally in 3 patients with abdominal symptoms (Table 1) . A 44 year-old female (Patient 2) with diabetes and old pulmonary TB, was receiving abdominal total hysterectomy for uterine myoma when nodular liver surface was observed by the surgeon during operation and the frozen section of liver biopsy revealed hepatic TB. The other patient (Patient 4) was a 76-year-old male with diabetes, hypertension, old stroke and old pulmonary TB, who was receiving surgical intervention for gastric angiodysplasia bleeding. Cirrhotic liver surface was observed during operation and liver biopsy revealed hepatic TB with positive TB-PCR. Patient 6 was a 20 year-old female who was receiving ultrasound-guided liver biopsy for evaluating living-related liver donation and liver TB was incidentally found.

Among these 10 patients, 4 patients had isolated hepatic TB (Patients 6, 7, 8, 9) , the other six patients had concomitant extra-hepatic TB infection. Coexistent pulmonary TB was found in 4

Table 1. Demographic characteristics in 10 adult patients with hepatic tuberculosis

Patient	Age(years) /Gender	erExtra-hepatic TB	Underlying infection	Clinical diseases	Abdomen image finding manifestations*	Diagnosis methods	Therapy	Outcome
1	55/M	Pulmonary TB	ESRD, HTN	1, 2	Echo, CT: liver tumor	Pathology via echo-guided liver biopsy	Anti-TB agents	Cured
2**	44/F	Pulmonary TB	DM, old pulmonary TB	7	None	Pathology via laparotomy	Anti-TB agents	Cured
3	55/F	GB, duodenum	HTN	1, 3, 5	Echo, CT: both lobe liver tumors, cholangiocarcinoma GB wall thickening	Pathology via echo-guided liver biopsy, AFB(+) Liver TB-PCR(+)	Anti-TB agents Surgical resection	Cured
4***	76/M	Pulmonary TB	DM, HTN, old, pulmonary TB old stroke	7, 8	Echo, CT: ascites, no liver tumor	Pathology via laparotomy Liver TB-PCR(+)	Anti-TB agents	Cured
5	44/M	GB, omentum	DM, HTN	1, 3, 5	Echo, CT: liver tumor with calcification cholangiocarcinoma and GB wall thickening Angiography: liver tumor	Pathology via laparotomy	Anti-TB agents Surgical resection	Cured
6****	20/F	—	Alcoholism	7	Echo, CT, MRI, Angiography: normal	Pathology via echo-guided liver biopsy	Anti-TB agents	Lost to f/u
7	71/F	— Gastric cancer	DM, HTN,	3, 4, 5, 6	Echo, CT: liver tumor laparotomy, AFB(+)	Pathology via	Anti-TB agents	Cured
8*****	41/M	—	Chronic hepatitis C,ulcerative colitis	2	Echo: Mild fatty liver	Pathology via echo-guided liver biopsy	Anti-TB agents	Cured
9*****	51/M	—	Bladder cancer	2, 3, 4	Echo: hepatosplenomegaly	Pathology via echo-guided liver biopsy	Anti-TB agents	Cured
10	70/F	Pulmonary TB, mesentery	Chronic hepatitis B,old pulmonary TB	1	Echo, CT: liver tumor with calcification Cholangiocarcinoma. L't IHDLiverstones Angiography: liver hypovascular tumor	Pathology via laparotomy TB-PCR(+)	Anti-TB agents Surgical resection	Cured

F: female, M: male, TB: tuberculosis, GB: gallbladder, ESRD: end stage renal disease, HTN: hypertension, DM: diabetes mellitus, Echo: echography, CT: computed tomography, CHD: common hepatic duct, CxR: chest X-ray, IHD: intra-hepatic duct, EGD: esophagogastroduodenoscopy, MRI: magnetic resonance imaging, AFB: acid-fast bacilli, TB-PCR: polymerase chain reaction for TB, Anti-TB: antituberculosis, f/u: follow-up.

*Clinical manifestations: 1. abdominal pain, 2. fever, 3. poor appetite, 4. body weight loss, 5. nausea or vomiting, 6. abdominal fullness, 7. incidental finding, 8. ascites

**Patient no.2: Nodular liver surface noted during operation (Abdominal total hysterectomy)

***Patient no.4: Cirrhotic liver surface noted during operation (Gastric angiodysplasia bleeding)

****Patient no.6: For living related liver donation evaluation

***** Patient no.8: Liver biopsy for pre-hepatitis C virus treatment evaluation

*****Patient no.9: Liver biopsy for fever evaluation

patients (Patients 1, 2, 4, 10), and one had active military pulmonary TB(Patients 4). Two patients had gallbladder(GB)involvement(Patients 3, 5). Involvement of duodenum (Patient 3), omentum (Patient 5) and mesentery (Patient 10)was

found in the other three patients respectively.

Image studies used for hepatic TB evaluation were abdominal sonograph (Figure 1), computed tomography(CT) (Figure 2), angiography,esophagogastroduodenoscopy(EGD)and



Fig.1. Sonographic finding in nodular hepatic tuberculosis (TB) varies from hypoechoic tumor with or without hyperechoic ring to hyperechoic tumor. This is the sonographic finding in a nodular hepatic TB which reveals a hypoechoic liver tumor with hyperechoic ring (white arrow).

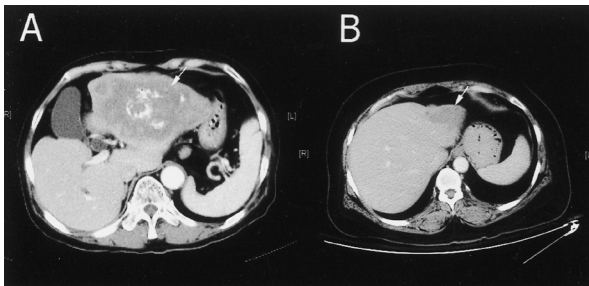


Fig.2. There is no characteristic feature on computed tomography scan specific for hepatic TB, even in the nodular form of liver mass. Figure 2A reveal solitary liver tumor with calcification (white arrow). Figure 2B reveals solitary liver tumor without calcification (white arrow).

magnetic resonance imaging (MRI). Abdominal sonography and CT were performed in 9 patients and their features are summarized in Table 1. There were variations such as solitary liver tumors with calcification (Patient 5, 10) or without calcification (Patient 1, 7), multiple liver tumors (Patient 3), GB wall thickening (Patient 3, 5), mild fatty liver (Patient 8), hepatosplenomegaly (Patient 9), ascites (Patient 4) and normal study (Patient 6). Hepatic angiography was performed for two patients (Patients 5, 10) that revealed hypovascular masses with calcification

in these 2 patients that were initially thought to be cholangiocarcinoma. EGD was performed in one (Patient 3) for gastrointestinal bleeding evaluation and ulceration with irregular base was found on the posterior wall of duodenal bulb. The subsequent endoscopic biopsy revealed granulomatous inflammation. This patient received liver biopsy, laparotomy with cholecystectomy and duodenorrhaphy, and all the pathological reports proved TB infection in the liver, the GB and the duodenum.

Patient 8 was a 41-year-old male with underlying chronic hepatitis C and ulcerative colitis, who received liver biopsy for pre-treatment evaluation for chronic hepatitis C. Liver pathology revealed hepatic TB with granulomatous inflammation and positive AFB stain. He received complete anti-TB therapy before anti-viral treatment. Patient 9 was a 51-year-old male with bladder cancer, who suffered from prolonged fever with unknown origin and abnormal liver function test. Ultrasound-guided liver biopsy was performed for fever evaluation and hepatic TB was diagnosed. The patient became afebrile and normalization of liver function test was noted after completion of anti-TB treatment.

All liver tissue underwent histopathological examination, AFB stain, and/or TB-PCR to confirm the diagnosis of hepatic TB. All patients had pathologic evidence of hepatic TB infection with the histopathological finding of epithelioid cell granuloma and central caseous necrosis, 30% were positive for TB-PCR, and 20% were positive for AFB stain. In addition, two GB TB were diagnosed by laparotomy and cholecystectomy, and one duodenal TB was diagnosed by EGD with biopsy. Six patients received surgical intervention and there were no significant postoperative complications or mortality.

All patients received antituberculosis therapy. Nine patients received at least 6 months of

antituberculosis drugs. A patient (Patient 6) took two months antituberculosis therapy but was lost to follow-up. All those patients who completed a full course of anti-TB treatments survived in the current study. The subsequent abdominal echo revealed negative findings in these 9 patients after completed antituberculosis therapy.

Discussion

TB spreads to the liver through the hepatic artery, the portal system and the lymphatic system. Liver TB commonly involves the hepatic parenchyma and sometimes the biliary tree. The presentations of liver TB are divided into three types: miliary hepatic TB, nodular hepatic TB and biliary tract TB^{6,8}. The miliary hepatic TB, which is hematogenously disseminated from the lungs via hepatic artery⁹, is the most common type of hepatic TB. Besides, TB can also spread through the portal system or the lymphatic system from the coexistent gastrointestinal tract TB¹⁰. However, among the 4 patients with coexisting pulmonary TB in the current study, only one of them had miliary pulmonary TB. This might result from non-specific symptoms and signs of hepatic TB. Besides, patients with pulmonary TB may not check liver status with routine examinations such as liver biochemistry tests, abdominal sonography or CT. Thus, the number of miliary hepatic TB patient is usually underestimated. Isolated hepatic TB nodules were presented in 4 patients, and one had multiple nodular pattern which involved both lobes of the liver.

Coexisting GB TB were found in two patients in our study. There are four possible different pathways for pathogenesis of GB TB. The hematogenous or lymphatic spread from the primary site, direct involvement or secondary involvement of liver TB, secondary excretion of AFB from the liver to the biliary tract, or secondary to periportal lymph node involvement¹¹⁻¹⁷. There was

no evidence that hepatic TB directly invaded GB according to pathological findings, nor coexistence of pulmonary TB in these two patients. Therefore, we believed that GB TB in our patients was either secondarily spread from hepatic TB via the hematogenous or lymphatic systems or via excretion of *M. tuberculosis* to the biliary tract. GB TB is usually presented with cholecystitis, obstructive jaundice or GB mass^{12,18}. None of these signs were found in our patients but only GB wall thickening was revealed by sonography.

The clinical presentation of hepatic TB is usually insidious and often non-specific^{19,20}. The non-specific nature of this disease often results in diagnostic delay. In our patients, the duration of symptoms and signs before hepatic TB diagnosis varied from one week to 6 months. Three patients were asymptomatic and hepatic TB was diagnosed incidentally. The clinical triad symptom of fever, abdominal pain and hepatomegaly in patients with hepatic TB has been described before^{19,20}. However, abdominal pain was found in 4 patients and fever was found in 3 from our series. Besides, only one of our patients (Patient 9) had hepatosplenomegaly, but no liver space-occupying lesion was found on abdominal sonography.

Image studies, such as abdominal sonography and liver CT, can detect liver solitary masses but there is no characteristic feature specific for hepatic TB, even in the nodular form of liver mass. Sonographic findings in nodular hepatic TB vary from hypoechoic tumors with or without hyperechoic ring to hyperechoic tumors^{21,22}. CT findings of hepatic TB may reveal hypodense mass and/or with hyperdense rim after enhancement study. Some hepatic TB might show heterogenous density with central necrosis or central calcification under CT scan^{21,23}. Maglante et al²⁴ reported that more than 50% of hepatic TB patients had calcification on image study. In our patients, nodular form hepatic TB presented hypoechoic

tumor in abdominal sonography and hypodense mass in CT studies. Liver tumors with calcification were noted in 2 of 5 patients with solitary or multiple nodular hepatic TB. Nevertheless, there was no typical hyperechoic rim in sonography or hyperdense rim in CT study. Angiography in two patients with nodular hepatic TB revealed hypovascular tumors with calcification, but these were not characteristic features suggestive of liver TB. Three patients were initially diagnosed as cholangiocarcinoma based on image studies. Hepatic TB was confirmed by pathological diagnosis, and 2 patients with solitary pseudotumor received left hepatectomy plus anti-TB therapy. Another one with multiple liver pseudotumors received anti-TB treatment. There was no liver tumor found on all image studies in the other 4 patients.

Therefore, pathologic and bacteriological evidence is necessary to confirm the diagnosis of hepatic TB. Due to low positive yield of culture and AFB stain, pathologic examination is the best way to confirm the diagnosis. In our study, of 10 patients with pathologically proven hepatic TB, only 2 had positive AFB stain. TB-PCR is a rapid and useful tool in the diagnosis of hepatic TB. In the literature, the diagnostic sensitivity of TB PCR in detecting culture confirmed and clinically diagnosed TB infection was 75.9% and 81.3% respectively. The specificity of TB PCR in diagnosing TB infection is 100%.²⁵ Diaz et al.²⁶ reported that over 50% of hepatic TB patients had positive TB-PCR but Popper et al.²⁷ and Ghossein et al.²⁸ reported that almost all patients with pathologic confirmation of hepatic TB had positive TB-PCR. TB-PCR was performed in 3 of our patients, and all of them had positive TB-PCR.

Conventional antituberculosis therapy for a minimum of 6 months is the recommended therapy once the diagnosis of hepatic TB is established²⁹. Nearly 100% of the disease can be completely

cured with anti-TB therapy. Since the definite diagnosis is difficult with image study alone and occult malignancy is possible, surgical intervention with hepatectomy is an alternative option in treating nodular hepatic TB when necessary. Xing et al. attained satisfactory results in his 8 hepatic TB pseudotumor patients that received segmentectomy or hepatectomy³⁰. In the current study, all patients received complete anti-TB therapy except for one patient who was lost to follow-up. Among them, two patients with solitary hepatic TB received left hepatectomy.

In summary, liver TB is a rare condition but a curable disease. The diagnosis for liver TB is difficult due to non-specific symptoms, signs, and variations on image findings. Therefore, determination of histopathology is necessary for definite diagnosis of liver TB but TB-PCR and AFB stain do help to confirm this. Once the diagnosis is made, the disease is usually associated with good prognosis and long-term outcome under complete anti-TB treatment.

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台灣南部之肝臟結核感染：15年臨床研究報告

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摘 要

肝臟結核的定義為肝臟中發現結核分枝桿菌感染，通常續發於肺結核或其他器官結核。此回溯性研究的目的是在於回顧本院肝臟結核的診斷與治療，並分析臨床表徵、影像學檢查及治療結果。從1992年1月至2006年12月，1251位病人經由病理診斷為結核菌感染，其中10位病人（5位男性，5位女性）診斷為肝臟結核。平均年齡為52.7歲（20~76歲）。臨床症狀包含腹痛（40%）、食慾不振（40%）、噁心或嘔吐（40%）、發燒（30%）及體重下降（20%）。3位病人為意外發現且無臨床症狀。4位病人為單獨性肝臟結核，而其他病人有合併出現肝外結核，有4位病人合併肺結核。9位病人的腹部超音波及電腦斷層檢查呈現單發性或多發性肝腫瘤。診斷方法包含超音波指引肝切片（50%），開腹探查術合併肝切片或肝切除（50%），肝組織結核菌聚合酵素鏈鎖反應陽性（30%），抗酸菌染色陽性（20%）。九位病人均接受完整抗結核菌治療並且治癒。總而言之，肝臟結核為少見但可治癒的疾病。由於無特異性的症狀與多變的影像學表現，診斷肝臟結核是困難的。組織學檢查對於確定診斷此疾病是必要的，但結核菌聚合酵素鏈鎖反應與抗酸菌染色可以提供幫助。肝臟結核經完整抗結核菌治療後通常有良好預後與治療效果。